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10/750,118	12/31/2003	Peter Sterling Mueller	893-2 CIP II /DIV	9765

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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/750,118	MUELLER, PETER STERLING	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,10,11,18,19,22,23,26-28 and 31-41* is/are pending in the application.

4a) Of the above claim(s) *1,3,5-7,10,11,18,19,22,23,26-28,31-34 and 39-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, 5-7, 10-11, 18-19, 22-23, 26-28 and 31-41 are presented for examination.

Applicant's Amendment filed August 8, 2006 has been received and entered into the present application.

Claims 1, 3, 5-7, 10-11, 18-19, 22-23, 26-28 and 31-41 are pending. Claims 1, 3, 5-7, 10-11, 18-19, 22-23, 26-28, 31-34 and 39-41 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b) and claims 35-38 remain under examination. Claim 35 is amended.

Applicant's arguments, filed August 8, 2006, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-38 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons set of record set forth at pages 3-4 of the previous Office Action dated May 3, 2006, of which said reasons are herein incorporated by reference.

Applicant traverses the present rejection, stating that sibutramine, sibutramine salts and derivatives of sibutramine are distinguishable from other molecules and are described in the instant specification. Applicant relies upon the disclosures of U.S. Patent Nos. 4,746,680; 4,929,629; and 5,436,272 for their teachings of sibutramine in its monohydrate form and enantiomers and analogues thereof. Applicant submits that a "derivative is defined as a chemical compound that may be produced

from another compound of similar structure in one or more steps, as in replacement of H by an alkyl, acyl or amino" (Applicant's remarks, page 10) and alleges that pages 12-13 of the instant specification define methods of preparation and the structures of sibutramine, sibutramine salts and derivatives of sibutramine. Applicant further relies upon the fact that the parent patents, U.S. Patent No. 6,323,242 and 6,696,495, each have claims directed to sibutramine derivatives, which were found to be described in such a way to apprise one of ordinary skill in the art as to what is encompassed by such a term.

Applicant's traversal has been fully and carefully considered in its entirety, but fails to be persuasive.

First, Applicant alleges that sibutramine, sibutramine salts and derivatives of sibutramine are described in the instant specification, but fails to provide any reference to portions of the instant specification that are specifically directed to defining "sibutramine derivatives" as claimed. In fact, the only reference Applicant provides is to the specification at pages 12-13 and page 15, which describe sibutramine monohydrate forms, enantiomers and analogues thereof, but fail to describe the scope of the genus of sibutramine derivatives as presently claimed.

It is further noted that the reliance and incorporation of U.S. Patent Nos. 4,746,680; 4,929,629; and 5,436,272 fail to remedy this deficiency in the disclosure because such U.S. Patents are directed to monohydrates, enantiomers and analogues of sibutramine, and not sibutramine derivatives. In fact, both the specification and the cited U.S. Patents are conspicuously silent in providing any guidance or direction to one of ordinary skill in the art to determine the metes and bounds of the claimed genus of sibutramine derivatives such that the skilled artisan would have been able to readily envisage the compounds intended by such a genus. Though Applicant cites to U.S. Patent Nos. 4,746,680; 4,929,629; and 5,436,272 to demonstrate that sibutramine derivatives were known and recognized in the art at the time of the invention, it remains that the art upon which Applicant relies is directed to monohydrates, enantiomers and analogues of sibutramine and not sibutramine derivatives. Accordingly, reliance upon

such art to demonstrate that the formation and preparation of sibutramine derivatives was well known in the art at the time of the invention is clearly not persuasive in establishing error in the propriety of the instant rejection because the cited art is not relevant to the claimed genus of sibutramine *derivatives* and, therefore, fails to establish that such sibutramine derivatives were well known in the art at the time of the invention.

As Applicant has noted, a derivative may be produced from another compound *of similar structure* (i.e., not necessarily the parent compound sibutramine, just a "related" compound) in one or more steps. However, Applicant has further failed to provide any definition of the compounds of similar structure to sibutramine that may be used to prepare the derivative compounds, how many steps away from the starter compound one may derive and what moieties on the parent molecule one may alter and still preserve the functionality of the compound to be the same, or substantially similar, to sibutramine. Though Applicant exemplifies a type of derivative, for example, wherein a hydrogen is replaced by an alkyl, acyl or amino, in the Remarks at page 10, it is noted that the instant specification fails to present any limiting, let alone exemplary, definition of the modifications that may be made to sibutramine *per se* or compounds of *similar structure* to produce compounds that would be considered "sibutramine derivatives" amenable for use in the present invention.

The fact that Applicant has failed to provide any degree of derivation that a compound may have from the parent compound and still be considered a pharmaceutically acceptable derivative suitable for use in the present invention is clear evidence that the skilled artisan would not have been reasonably apprised of the scope of the claimed genus of "sibutramine derivatives" because there is no guidance as to what elements of the compound must be preserved in order to retain its function in achieving the claimed objective. Moreover, due to the very complexity of chemical compounds in general, and further in view of the fact that compounds that demonstrate at least some degree of structural similarity differ radically in pharmacologic properties, random modifications of the compounds to produce a "derivative", in the

absence of any direction as to the locations suitable for such modifications and/or the number of times and/or the manner in which the compound could conceivably be modified, would have been reasonably expected to alter the structure and function of the molecule due to, for example, reactivity of side groups or steric effects, which would have been reasonably expected to constructively alter the conformation and reactivity of the whole molecule.

In view of this knowledge, and absent any direction or guidance by Applicant to reasonably apprise the skilled artisan of the metes and bounds of the genus of sibutramine derivatives, one of skill in the art would have been obligated to execute hit or miss testing practices to determine those sibutramine derivative compounds amenable for use in the present invention. The need for testing amongst widely varying species of compounds to determine the full scope of the claimed genus of sibutramine derivatives clearly demonstrates that Applicant was not in possession of the full scope of the genus now presently claimed. As stated in the MPEP §2163, "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention."

Moreover, it is noted that a "derivative", as defined by Applicant at page 10 of the Remarks, and an "analogue" compound are not one and the same. Applicant's attention is directed to Technical Reports (Vol.2, No. 16), *Glossary of Terms Used in Medicinal Chemistry* (1998), which defines an analog as "a drug whose structure is related to that of another drug but whose chemical and biological properties may be quite different" (page 2). In view of such, Applicant's reliance upon U.S. Patents defining sibutramine analogs is not sufficient to provide adequate written description of sibutramine derivatives.

Lastly, it is noted that Applicant's reliance upon the issuance of U.S. Patent Nos. 6,323,242 and 6,696,495 with the term "sibutramine derivatives" has been fully and carefully considered, but is not

persuasive. It is noted that each case before the Patent Office is decided on its own merits and in preponderance of the evidence, amendments and arguments presented in each unique case. Decisions made in previous cases before the Office are not necessarily binding to the course of prosecution in a distinctly different case.

For these reasons provided *supra*, and those previously made of record at pages 3-4 of the previous Office Action dated May 3, 2006, rejection of claims 35-38 is proper and is **maintained**.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-38 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of sibutramine, does not reasonably provide enablement for the use of derivatives of sibutramine, for the reasons of record set forth at pages 4-10 of the previous Office Action dated May 3, 2006, of which said reasons are herein incorporated by reference.

Applicant is notified that the present rejection is herein maintained insofar as the instant specification fails to reasonably provide enablement for the use of derivatives of sibutramine. The holding of a lack of enablement for the use of compounds possessing the pharmacological activity of inhibiting dopamine, serotonin and norepinephrine is hereby withdrawn in view of Applicant's remarks and a reconsideration of the claim language. Accordingly, Applicant's remarks regarding the enablement of compounds that inhibit dopamine, serotonin and norepinephrine will not be further considered herein as this aspect of the rejection has been withdrawn.

Applicant traverses the instant rejection, stating that both the parent patents and the referenced patents provide considerable direction and guidance in the specification as to how one would prepare

derivatives of sibutramine. Applicant relies upon the instant specification at pages 12-13 and 15, in addition to the various case study examples at pages 19-38 to support the assertion that adequate guidance and direction has been provided to the skilled artisan. Applicant disagrees with the Examiner's conclusion that one of ordinary skill in the art would have been burdened with undue painstaking experimentation study to determine all of the types and derivatives of sibutramine compounds that would be enabled by the present specification and, thus, useful for the instant invention by relying upon the disclosures of U.S. Patent Nos. 4,746,680, 4,929,629 and 5,436,272 to enable the preparation and use of derivatives of sibutramine.

Applicant's traversal has been fully and carefully considered in its entirety, but fails to be persuasive.

Applicant's specification and disclosure fails to present any guidance or direction as to how one of ordinary skill in the art would go about the synthesis of any one or more sibutramine derivatives, with the exception of sibutramine *per se* or salts of sibutramine. Though Applicant references three U.S. Patents at pages 12-13 and 15 of the specification, such as, e.g., 4,746,680; 4,929,629; and 5,436,272, it is noted that these documents are not explicitly directed to "sibutramine derivatives", but rather are directed to monohydrate forms, enantiomers and analogs of sibutramine, and, therefore, cannot be relied upon as enabling support to teach identity of and methods of synthesizing the presently claimed sibutramine derivatives such that one of ordinary skill in the art would have been able to rely upon such documents in order to obviate the need to execute an undue level of experimentation to accomplish such objective(s).

Moreover, Applicant has defined, on the record, that a derivative is defined as a chemical compound that may be produced from another compound of similar structure in one or more steps, as in the replacement of hydrogen by an alkyl, acyl or amino. Please see page 10 of Applicant's remarks. However, Applicant has not only failed to provide any disclosure of guidance as to what compounds are, in fact, intended by the genus of "sibutramine derivatives", such as by name(s), chemical formula(a),

structure-activity relationship(s), physical properties, etc., Applicant has also conspicuously failed to identify any subset of starting compound(s) from which the derivative may be obtained (noting, also, that Applicant states that the derivative may be produced from *another compound of similar structure*, and not necessarily the parent compound *per se*, i.e., in this case, sibutramine) and what, if any, modifications may be made, and how such modifications would be made, to such starting compounds to produce compounds "derived" from sibutramine such that the skilled artisan would have been imbued with at least a reasonable expectation of success in identifying and preparing compounds that are (1) derivatives of sibutramine and (2) useful for achieving the presently claimed therapeutic objective(s) of treating the symptoms of reflex sympathetic dystrophy syndrome or complex regional pain syndrome.

Furthermore, given the fact that Applicant has failed to provide any limiting, let along exemplary, definition of compounds that would be considered sibutramine derivatives, one of ordinary skill in the art would conceivably need to test hundreds, if not thousands or even millions, of compounds showing any remote relationship to sibutramine to determine if such "derivatives" of sibutramine showed any activity in treating the complex syndromes claimed, i.e., reflex sympathetic dystrophy syndrome or complex regional pain syndrome. Since the instant specification fails to provide any criteria or protocol with which to make such a determination, such random speculation and hit or miss testing clearly amounts to an undue level of experimentation, absent factual evidence to the contrary. Additionally, even if Applicant were to argue that the claimed "sibutramine derivatives" must show some similar structural properties to sibutramine *per se* and, therefore, would be expected to show a similar level of activity in treating the claimed syndrome(s) based upon this similar structural property, Applicant is reminded that even compounds with similar structural properties do not necessarily have the same level of activity, since structural composition is simply representative of the way the atoms are bonded and arranged in space but does not account for differences in molecular size, shape, ionization, charge distribution, solubility, interatomic distance, geometric and stereochemical configurations, or the rigidity and flexibility of the

molecule, each of which affects the compound's activity. Accordingly, absent any further direction or guidance provided by Applicant either in the instant specification or in the remarks as to how the present disclosure reasonably enables the preparation and use of the full scope of "sibutramine derivatives" as claimed, one of ordinary skill in the art would have no alternative recourse but to undertake an exhaustive, and, thus, unduly burdensome, search for ways to synthesize embodiments of the claimed sibutramine derivative compounds suitable for use in practicing the claimed invention, particularly since the skilled artisan is faced with such a breadth and variation of compounds that a method for synthesizing any one such compound would not necessarily be useful or amenable for synthesizing any one or more other compounds within the scope of compounds actually claimed. As a result, the present conclusion of a lack of enablement for these aspects of the claimed invention remains proper.

For these reasons, and those previously made of record at pages 4-10 of the previous Office Action dated May 3, 2006, rejection of claims 35-38 remains proper and is **maintained**.

Conclusion

Rejection of claims 35-38 remains proper and is **maintained**.

No claims of the present application are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the

mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leslie A. Royds
Patent Examiner
Art Unit 1614

July 2, 2007

7/2/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER